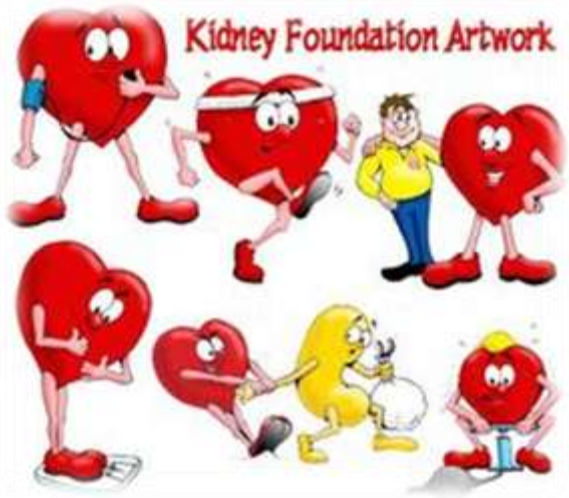
Renal Biomarkers of Cardio-Renal Syndrome

Mostafa Abdel_Salam Mohamed, MD
MUH



Organ Crosstalk

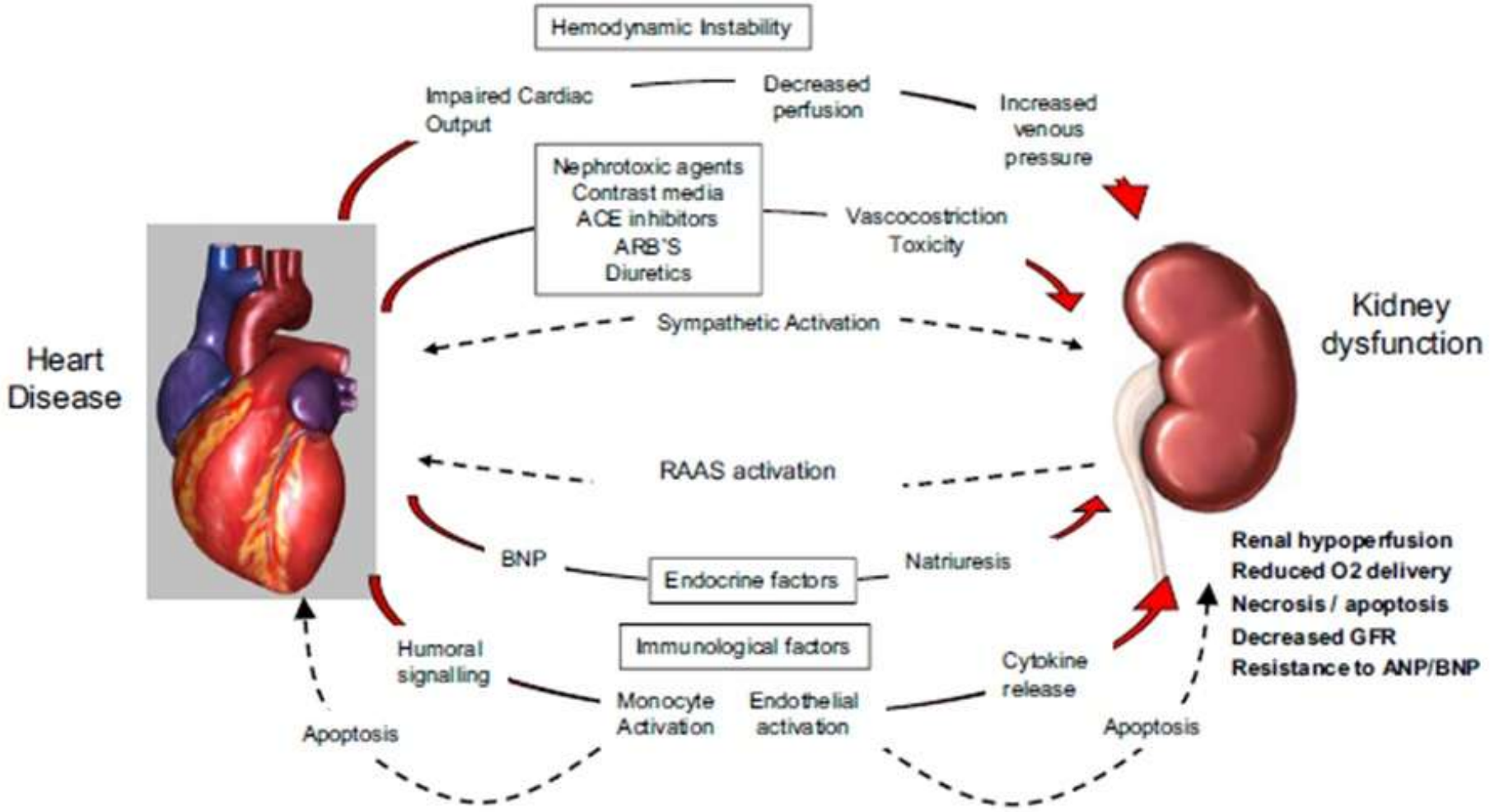






Combined disorders of heart and kidney are classified as cardiorenal syndromes

Type	Known as	Description
Type 1	Acute	Acute HF results in AKI
Type 2	Chronic	Chronic cardiac dysfunction causes progressive CKD
Type 3	Acute renocardiac	Abrupt and primary worsening of kidney function causes acute cardiac dysfunction which may present as cardiac failure
Type 4	Chronic renocardiac	Primary CKD contributes to cardiac dysfunction which may be manifested by coronary disease, cardiac failure, or arrhythmia
Type 5	Secondary	Acute or chronic systemic disorders that cause both cardiac and renal dysfunction

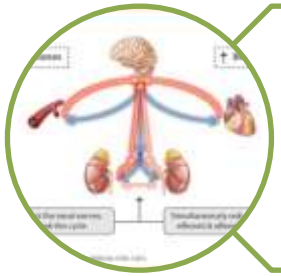


Schrier RW, Masoumi A, Elhassan E. Role of vasopressin and vasopressin receptor antagonists in type i cardiorenal syndrome. Blood Purif. 2009;27:28e32.

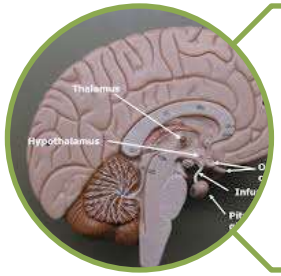
Al-Hesayen A, Parker JD. The effects of dobutamine on renal sympathetic activity in human heart failure. J Cardiovasc Pharmacol. 2008;51:434e436



Hemodynamic dysfunction



Neurohormonal activation



Hypothalamic–pituitary and humoral stress reaction

Al-Hesayen A, Parker JD. The effects of dobutamine on renal sympathetic activity in human heart failure. J Cardiovasc Pharmacol. 2008;51:434e436



To limit the injury at the kidney level

An early diagnosis is necessary



This is not the case when using the creatinine parameter.

There is actually a delay of approximately 48 h between the kidney injury and the rise in serum creatinine level.

Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis Jun. 2009;53(6):961–73.



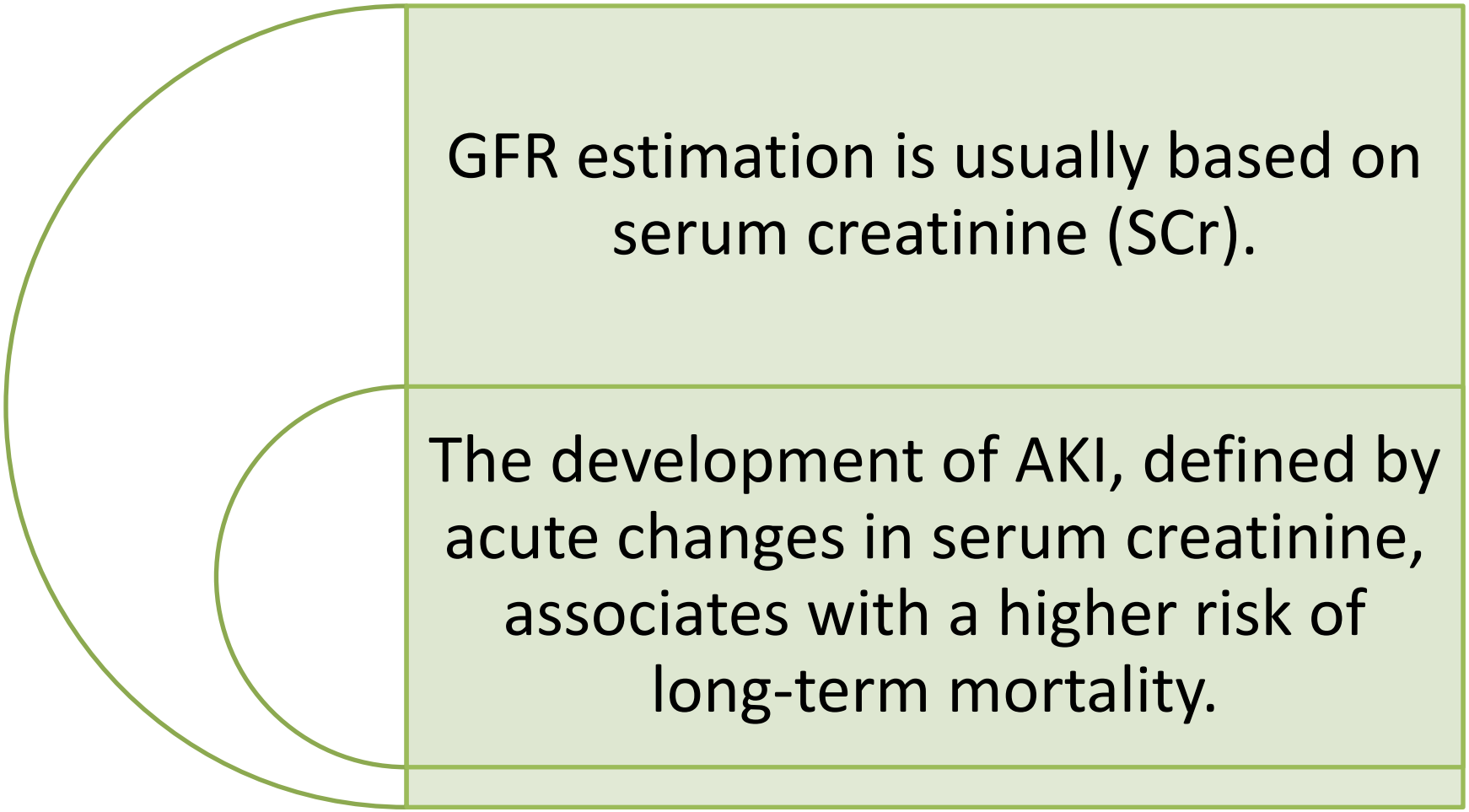
Several urinary and serum biomarkers of structural kidney injury have been investigated to identify KI earlier, in order to improve the diagnosis and the treatment of KI and to get a good prognostic evaluation of patients admitted to the hospital.

KI Biomarkers' Characteristics

- Noninvasive.
- Easy.
- Rapidly and reliably measured.
- Highly sensitive.
- Strong biomarker performance on
- statistical analysis.
- Highly specific for AKI.

Crit Care Med 2008. Vol. 36, No. 4 (suppl.)

Creatinine



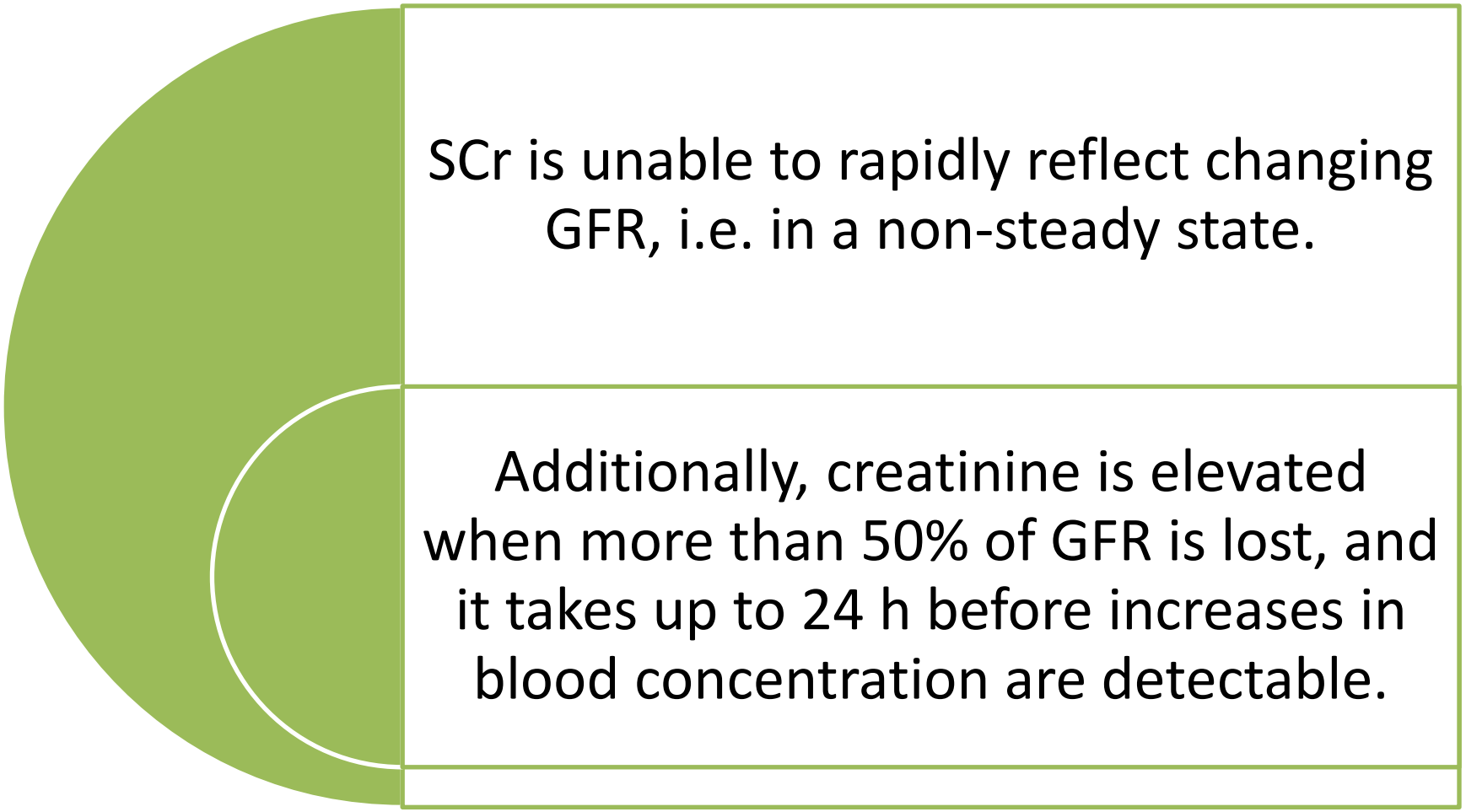
Bellomo R. Acute renal failure. Semin Respir Crit Care Med Oct. 2011;32(5):639–50.

SCr is known to be a rather insensitive GFR biomarker.



Many factors independent of kidney function affect creatinine, including: age, gender, muscle mass and metabolism (both already modified during AHF and AKI periods), medications, and level of hydration

Akhter MW, Aronson D, Bitar F, et al. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. Am J Cardiol Oct. 1 2004;94(7):957–60.


SCr is unable to rapidly reflect changing GFR, i.e. in a non-steady state.
Additionally, creatinine is elevated when more than 50% of GFR is lost, and it takes up to 24 h before increases in blood concentration are detectable.

Moreover, SCr is not exclusively cleared by glomerular filtration but is also partially secreted by renal tubules. This well known phenomenon may account for substantial GFR overestimation SCr level is more a marker of renal function than kidney injury.

Albuminuria



In CKD, albuminuria has been advocated as an important therapeutic target. The degree of reduction in albuminuria was strongly correlated with cardiovascular outcome and, more importantly, incident HF.

Albuminuria	Reflects glomerular damage
	A marker of generalized endothelial dysfunction
	Reflecting the pathophysiology of the interactions between the cardiovascular and renal systems, but only in chronic circumstances.

Not sensitive

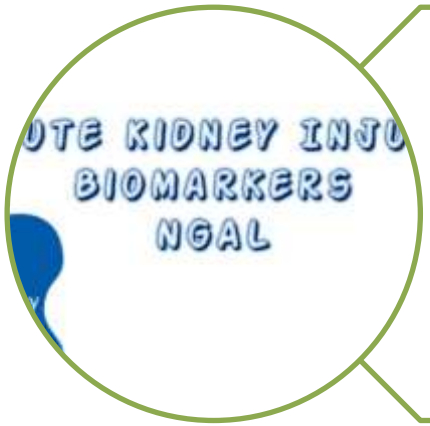
Not specific

Damman K, Navis G, Smilde TDJ, et al. Decreased cardiac output, venous congestion and the associationwith renal impairment in patientswith cardiac dysfunction. Eur J Heart Fail Sep. 2007;9(9):872–8.
Jackson CE, Solomon SD, Gerstein HC, et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet Aug. 15 2009;374(9689):543–50.
Masson S, Latini R, Milani V, et al. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure Trial. Circ Heart Fail Jan. 1 2010;3(1):65–72.

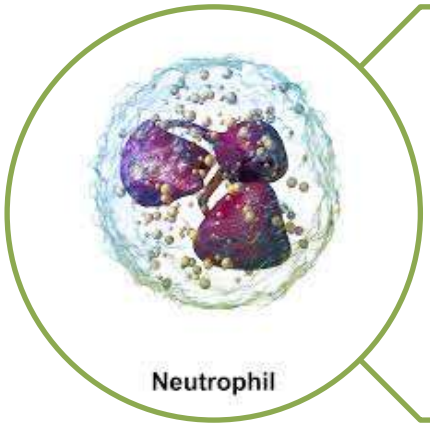
Neutrophil gelatinase-associated lipocalin (NGAL)

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2 (LCN-2), is a small 25-kDa protein with 178 amino acids.

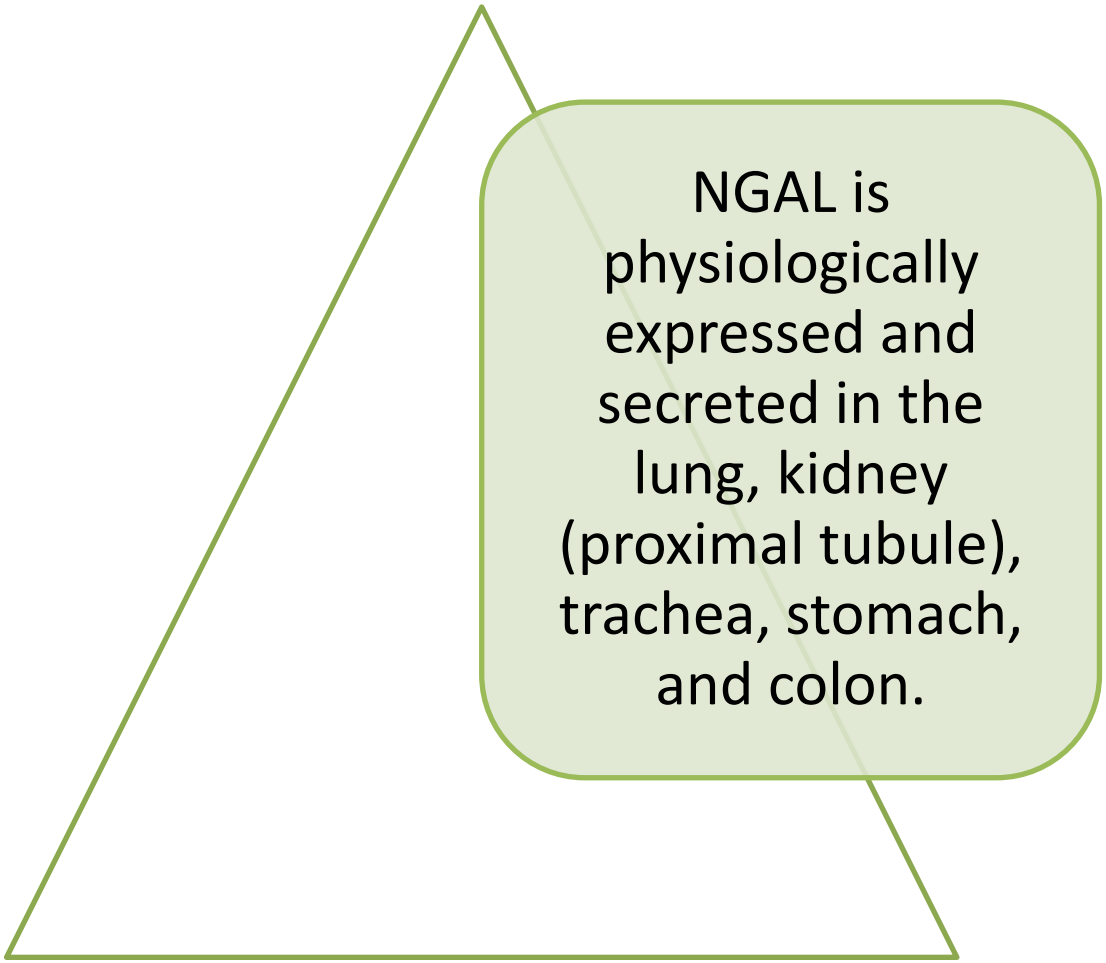
It belongs to the lipocalin family of proteins. Because of its small molecularweight, plasma NGAL is fully filtered through the glomerulus and totally reabsorbed in the tubules



NGAL has been shown to be involved in immune modulation, inflammation, and neoplastic transformation.



It is expressed in immature neutrophils and epithelial cells .


NGAL is physiologically expressed and secreted in the lung, kidney (proximal tubule), trachea, stomach, and colon.

NGAL is thought to be bacteriostatic in pathological states by forming complexes with iron-binding siderophores.

The physiological role of NGAL in renal ischemia or toxin induced kidney injury may be to decrease injury by reducing apoptosis and increasing the normal proliferation of kidney tubule cells

NGAL in plasma is generated by a systemic inflammation, which induces NGAL synthesis by extrarenal tissues and the release of NGAL from neutrophils.

Masson S, Latini R, Milani V, et al. Prevalence and prognostic value of elevated urinary albumin excretion in patients with chronic heart failure: data from the GISSI-Heart Failure Trial. Circ Heart Fail Jan. 1 2010;3(1):65–72.

The decrease in GFR induces an increase in plasma NGAL concentration.

Urinary NGAL increases due to an impaired reabsorption of the filtered load, an increased synthesis from stressed tubular cells in the distal nephron and a release by infiltrating neutrophils

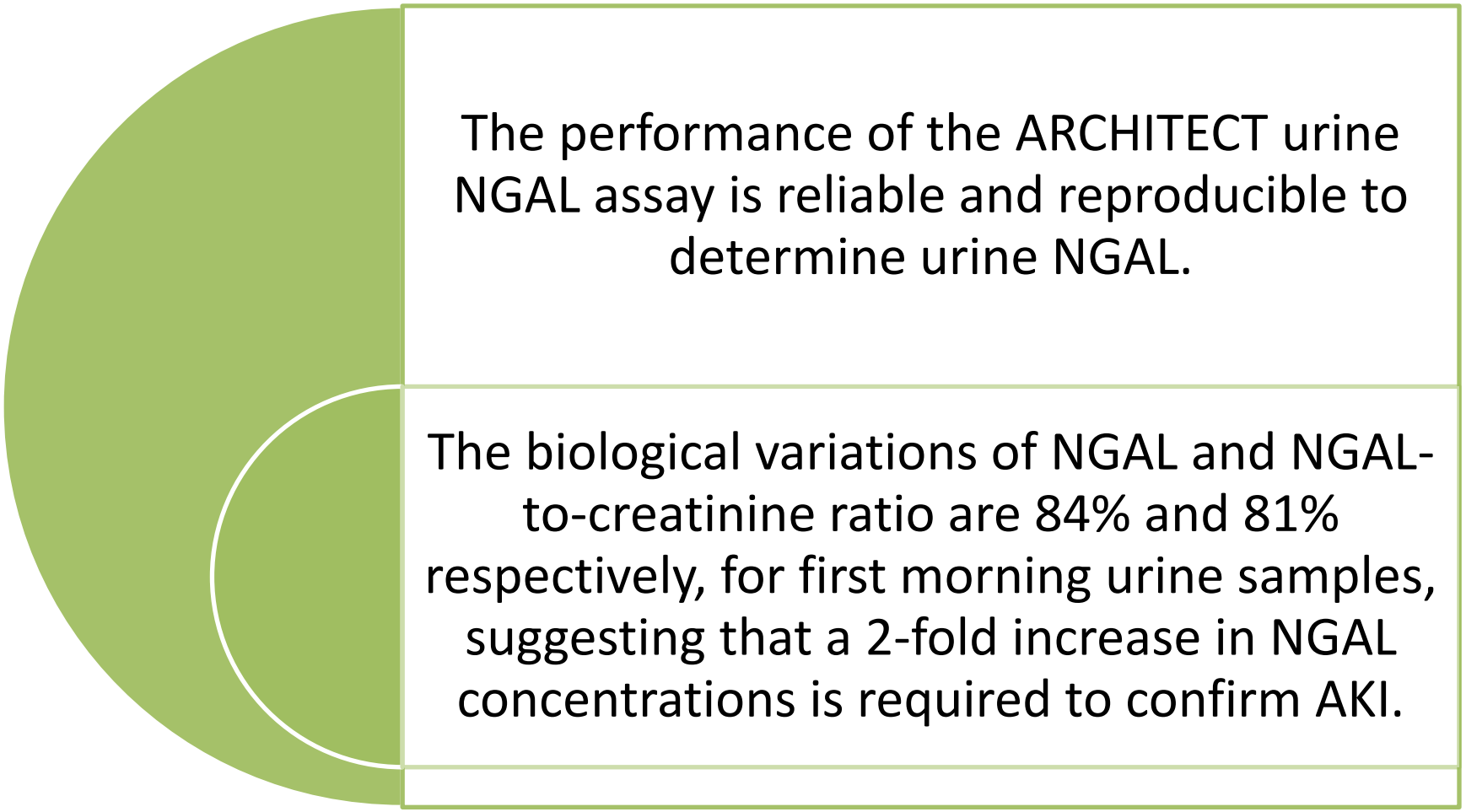
The pathophysiological role in HF has not been well described.

The physiological role of NGAL in the mechanism of renal and cardiac dysfunction should be associated with the inflammatory process.

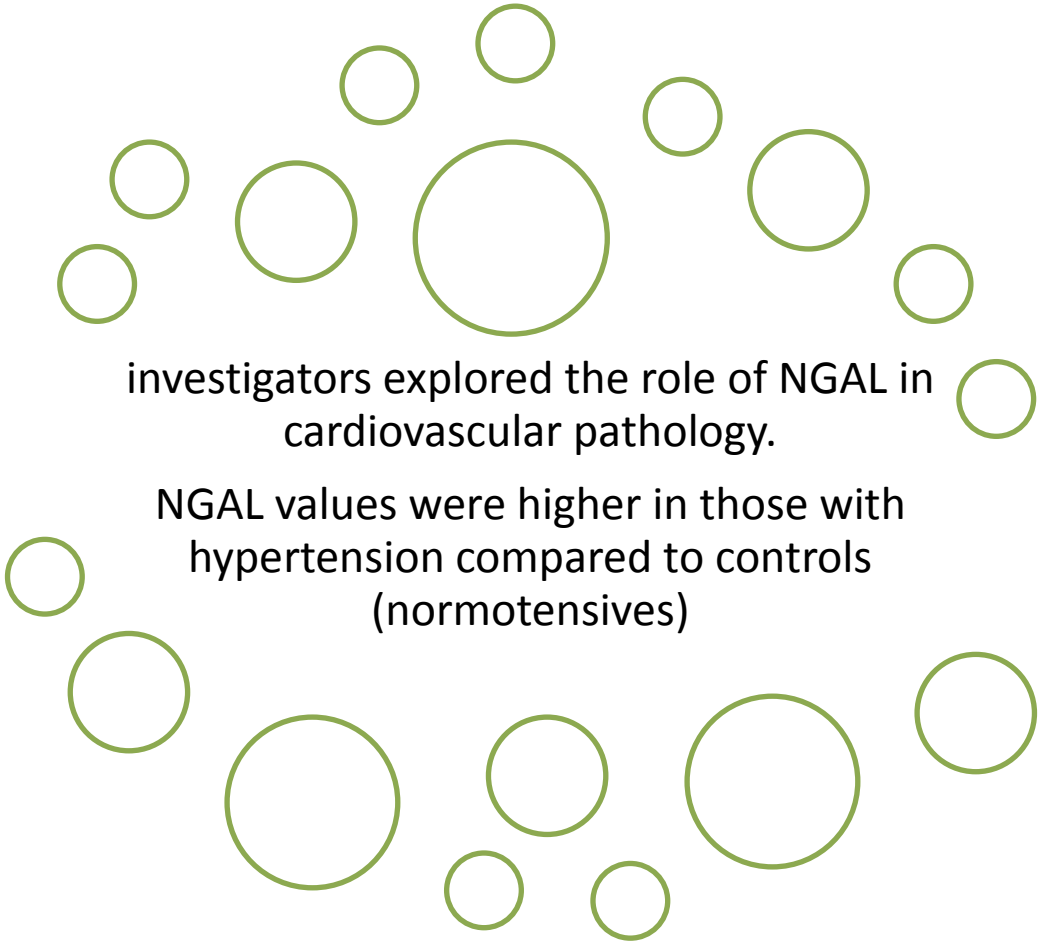
Jackson CE, Solomon SD, Gerstein HC, et al. Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet Aug. 15 2009;374(9689):543–50.

Plasma NGAL levels are less specific for renal disease, as higher levels are also found in inflammation, sepsis, or cancer. In patients with chronic heart failure (CHF), associated with an inflammatory state and increased oxidative stress,

The analysis of NGAL levels should be interpreted carefully. Urine levels are much less affected by these situations, since the NGAL that appears in the urine is secreted only from the tubules


The performance of the ARCHITECT urine NGAL assay is reliable and reproducible to determine urine NGAL.
The biological variations of NGAL and NGAL-to-creatinine ratio are 84% and 81% respectively, for first morning urine samples, suggesting that a 2-fold increase in NGAL concentrations is required to confirm AKI.

Plasma NGAL may increase its usefulness in the diagnosis and prevention of CRS if a curve of plasma values in function of time is used rather than a single plasma measurement.



investigators explored the role of NGAL in cardiovascular pathology.

NGAL values were higher in those with hypertension compared to controls (normotensives)

NGAL in AKI

- Serum and urine NGAL have been well demonstrated to increase dramatically in renal failure underlining their potential role as a marker for kidney injury

Haase et al., 2011 demonstrated that

- NGAL was an early predictor of subclinical AKI, with early elevations in plasma NGAL levels compared to serum creatinine.
- Moreover, in-patient mortality was highest in those patients with elevated NGAL levels, with or without elevated serum creatinine

NGAL in HF

In a study where patients are admitted with AHF, elevated plasma NGAL with a cut-off value of 170 ng/ml at time of admission was associated with development of type 1 CRS within 48 to 72 h.

Others studies have found that among patients admitted for ADHF, those who subsequently developed WRF (defined as creatinine rise N0.3 mg/dL) had significantly higher NGAL values than those who maintained steady renal function.

SerumNGAL is a robust marker for detecting early AKI and carries high diagnostic and prognostic usefulness both in ADHF and on hospitalized patients.

Many studies have shown that

- NGAL rises 24 to 48 h before creatinine, and thus shows promise in being a powerful marker for early detection of kidney damage .

some studies demonstrated that

- urinary NGAL did not reliably predict persistent renal impairment or all-cause mortality in ADHF

Verbrugge FH, Dupont M, Shao Z, et al. Novel urinary biomarkers in detecting acute kidney injury, persistent renal impairment, and all-cause mortality following decongestive therapy in acute decompensated heart failure. J Card Fail Sep. 2013

Some authors have suggested that	serum and urinary NGAL represent different aspects of the nephron's function
Whereas	higher serum NGAL correlates well to reduced glomerular filtration function
	urinary NGAL is more a marker of impaired natriuresis and diuresis in the setting of ADHF

Cystatin C



Another marker also has its place in the early detection of AKI with performance superior to creatinine.

This biomarker is Cystatin C (CysC). This marker is a low-molecular-weight protein (13.3 kDa) and belongs to the family of cysteine proteinase inhibitor proteins .

Cys C	half-life of 1.5 h (compared with 4 hours for creatinine).
	Cys C concentration increases earlier than creatinine concentration, enabling faster identification of AKI.

CysC may play

a direct physiological role and influence ventricular remodeling due to its origin (cysteine proteases inhibitors).

CysC has been implicated in

pathological left ventricular remodeling in HF.

Cystatin C in HF

- CysC appears to be a useful marker of early AKI in patients hospitalized for AHF.
- A decline in renal function detected by Scys C during the first 48 h after hospitalization occurs frequently in AHF.
- This increase can predict the development of CRS type 1 and has a negative impact on prognosis .

Haase et al.

- demonstrated that plasma NGAL and SCysC were the strongest predictors of developing AKI (defined with RIFLE criteria) in patients post-cardiac surgery.

Kidney injury molecule-1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is

a transmembrane glycoprotein with an immunoglobulin and mucin domain.

KIM-1 is

markedly induced in response to renal injury and is expressed on the proximal tubule apical membrane.

Lassus JPE, Nieminen MS, Peuhkurinen K, et al. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J Nov. 2 2010;31(22):2791–8.

Data suggests that KIM-1 expression is protective during early injury, but not in chronic disease states.

KIM-1 plays	a role in kidney proximal epithelial cells transformation into phagocytes.
	As a consequence of its role, the clearance of dead cells increases and protects the kidney early after injury.

A number of studies have demonstrated KIM-1 to be

- a marker of AKI occurring after cardiopulmonary by-pass surgery (CPB) and cardiac catheterization.

Urinary KIM-1 was also associated with

- increased risk of death or hospitalization, independent of GFR in patients with chronic heart failure

KIM-1 has also been associated with the risk of incident congestive HF.

urinary levels of KIM-1 in the immediate postoperative CPB period provide additional prognostic information for 3-year mortality risk in patients with and without clinical AKI.

Ruan Z-B, Zhu L, Yin Y-G, Chen G-C. Cystatin C, N-terminal probrain natriuretic peptides and outcomes in acute heart failure with acute kidney injury in a 12-month follow-up: Insights into the cardiorenal syndrome. J Res Med Sci May 2014;19(5)

Fatty acid binding protein (FABP)

Fatty-acid binding proteins (FABPs) are a family of 15-kDa cytoplasmic proteins that are involved in the intracellular transport of long chain fatty acids.

Two types of FABPs are interesting in AKI management.

The first is the kidney heart-type (H-FABP), located in the distal tubular cells

the second is the liver-type (L-FABP), which is located in the proximal tubular cells.

L-FABPs may also have a role in the reduction of cellular oxidative stress, binding fatty acid oxidation products, and limiting the toxic effects of oxidative intermediates on cellular membranes.

Urinary L-FABP is undetectable in healthy control urine.

Under ischemic conditions, the proximal tubular reabsorption of L-FABP is reduced.

The performance of urinary L-FABP has been demonstrated in small series of intensive care unit (ICU) patients with promising results to predict outcome

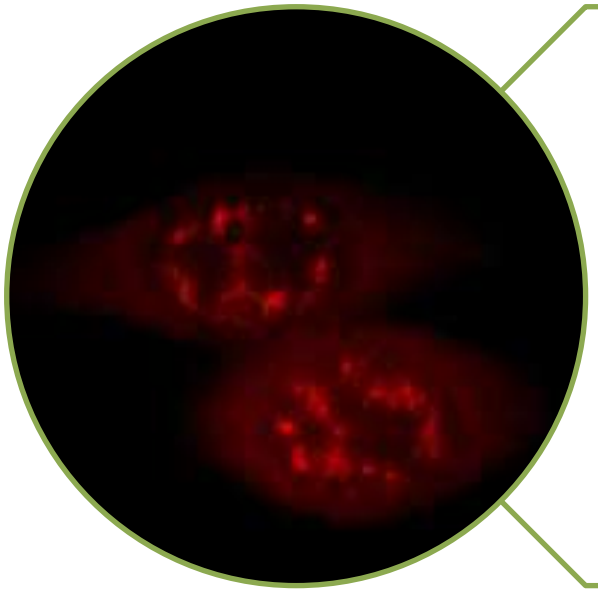
N-acetyl-β-D-glucosaminidase (NAG)

The enzyme N-acetyl-β-D-glucosaminidase (NAG) is a lysosomal brush border enzyme found predominantly in proximal tubular cells. It has a large molecular weight (N130 kDa) and is therefore not filtered by glomerular filtration.

It sheds into the urine in response to tubular injury. When combined, NAG and L-FABP could detect AKI with higher accuracy than either biomarker measurement alone .

urinary NAG	is increased in postoperative AKI patients with cardiac surgery but not in stable renal function.
	In patients with HF, is associated with an increased risk of death or HF hospitalizations regardless of GFR.

Interleukin-18 (IL-18)

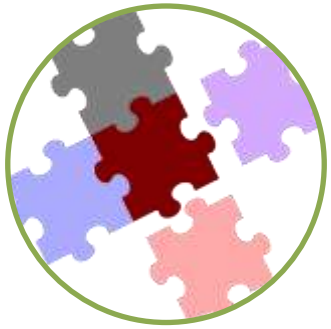


Interleukin-18 (IL-18) is an 18-kDa pro-inflammatory cytokine originating from proximal tubular cells.

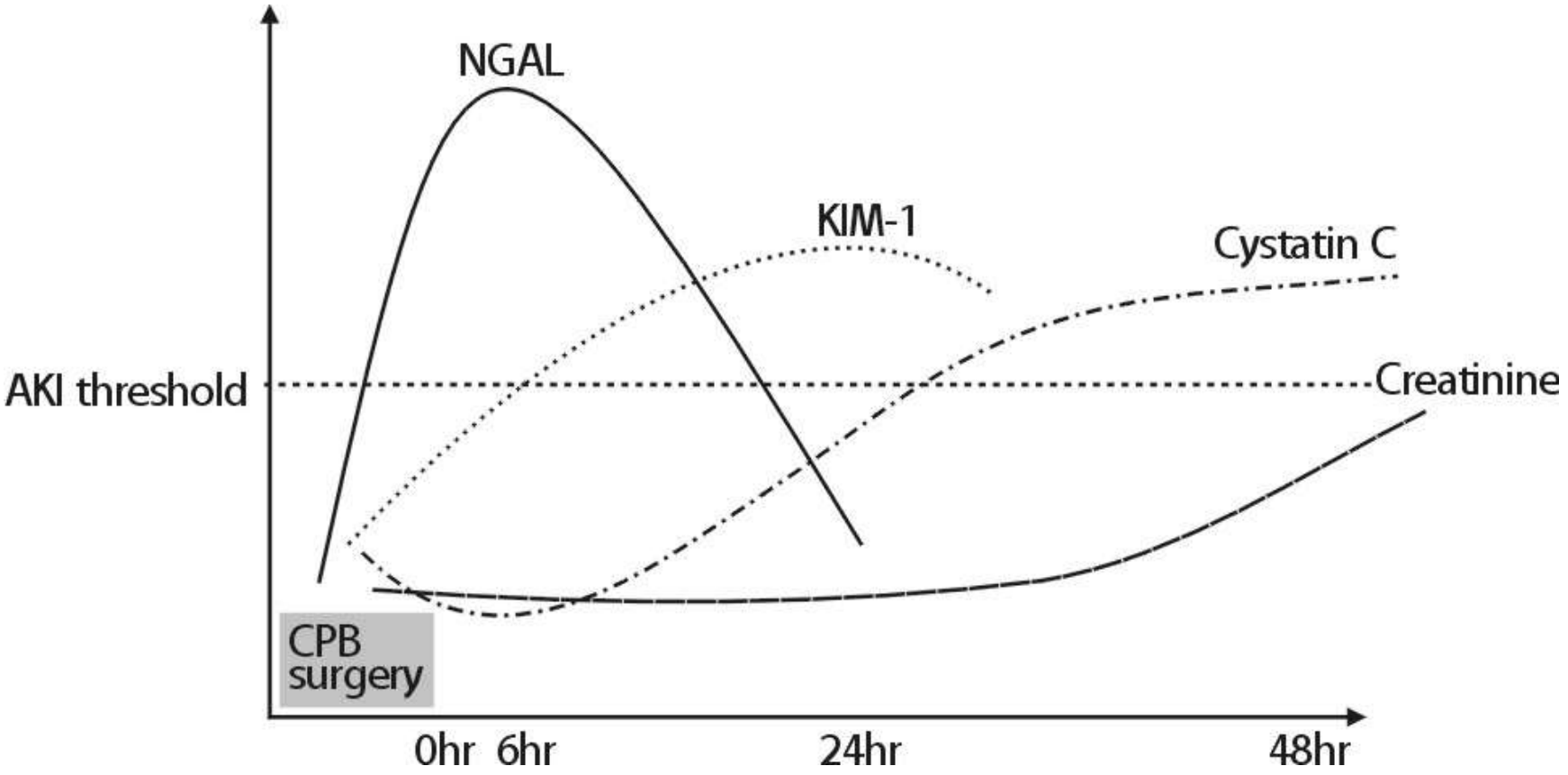
It is detected in the urine after acute proximal tubular damage. It probably has a role inmediation of ischemic renal failure.

called the inflammasome.

Few data highlighted the role of IL-18 as predictor of outcome in ischemic heart disease and, as such, as predictor of the incidence of HF.



Combinations of renal biomarkers



Representative curves showing changes in biomarker levels for the detection of acute kidney injury (AKI) after cardiopulmonary bypass (CPB) surgery (adapted from a previous study

McIlroy DR, Wagener G, Lee HT: Biomarkers of acute kidney injury: an evolving domain. Anesthesiology ,

Cardiac	Renal
Currently available biomarkers	
• Electrocardiogram	• Urine output
• Echocardiography	• Serum creatinine
• Troponins	• Blood urea
• Natriuretic peptides	• Urine microalbumin
• Myoglobin	• Urine protein creatinine ratio
• Creatinine phosphokinase	• Abdominal ultrasound
• LDH	
Emerging biomarkers	
• ssTnI	• NGAL
• GDF 15	• Cystatin C
• ST2	• KIM-1
• MR proANP	• IL-18
• FABP	• L-FABP
• Vitamin D	• NAG
• FGF 23	• Netrin 1
• Isoprostanes	• Monocyte chemotactic peptide 1
	• Vanin 1

LDH – Lactate dehydrogenase, ssTnI – slow skeletal troponin I, MR proANP – mid regional pro atrial natriuretic peptide, FABP – Fatty acid binding protein, FGF 23 – Fibroblast growth factor 23, GDF 15 – Growth differentiation factor 15, KIM-1 – Kidney injury molecule-1, NGAL – Neutrophil gelatinase associated lipocalin, NAG – N-acetyl-beta-D-glucosaminidase.



Mansoura Nephrology and Dialysis unit

MNDU

